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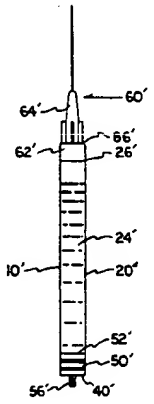
## (54) Method of terminal steam sterilization.

(57) A method for terminal steam sterilization of a pre-filled plastic or glass syringe or cartridge is disclosed, said method comprising the steps of: maintaining a head space in the syringe or cartridge of not exceeding about 10% volume; providing at least about 2%, preferably about 10%, leeway for the plunger therein to slide in response to pressure differential; and in the case of a plastic syringe or cartridge sterilizing the syringe or cartridge at an autoclave pressure that is less than the internal pressure of the syringe or cartridge content; or in the case of a glass syringe or cartridge sterilizing the syringe or cartridge at an autoclave pressure that is less than, equal to or greater than the internal pressure of the syringe or cartridge content.

FIG. 5

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The present invention relates to a process for terminal sterilization of pre-filled plastic and glass syringes and cartridges containing liquid pharmaceutical, biological or veterinary products. More particularly, the invention relates to a process for terminal sterilization of liquid contrast media for parenteral administration contained in plastic and glass syringes and cartridges.

The prior art discloses containers, apparatus and processes for steam-sterilization of products and medical devices used in the health and medical fields where sterility is an absolute requirement. Generally speaking, such sterilization may be accomplished by steam-sterilizing the containers/packages and contents separately, followed by placing the contents into the containers/packages and hermetically sealing the same for use at a later time. Such processes, however, carry the risk of contamination and introduction of pyrogens during the transfer of the products into their containers/packages. The trend in the pharmaceutical industry is toward terminal steam-sterilization wherein the contents are sterilized within their containers/packages.

In the process of such steam-sterilization, the pre-filled containers/packages are placed in an autoclave and are subjected to operational cycles which include: purging air from the autoclave chamber by forcing saturated steam therethrough at about a pressure of 1 to 20 psig at a temperature of about 100 °C to 150 °C for about a minute to 30 minutes; further introducing steam into the autoclave chamber so that the temperature of about 100 °C to 125 °C is reached therein; maintaining the temperature for a time sufficient to sterilize the content of the autoclave; cooling the autoclave and removing the containers/packages therefrom. Typical containers containing parenteral formulations, such as glass ampoules, stoppered vials and bottles are able to withstand the pressure differentials between the containers and the autoclave chamber created by the operational cycles of the sterilization process. However, pre-filled syringes and cartridges made of plastic or glass do not tolerate significant pressure differential when the internal pressure is greater than the external; such pressure differential results in an unacceptable number of container/package failures that will occur either during the heating phase or the cooling phase of the autoclave cycle.

In the case of glass syringes and cartridges such failure typically will be in the form of plunger blow-out during the heating phase caused by the sum total of product vapor pressure, thermal expansion of the product and the pressure increase of the gas occupying the head space in the container. Should seal integrity be maintained through the heating phase, failure may occur during the cool-down phase of the sterilization cycle when the liquid content in the containers is at or above its boiling point, creating pressures within the containers greater than one atmosphere while the pressure in the autoclave drops to one atmosphere.

In the case of plastic syringes and cartridges, in addition to container/package failure by plunger blow-out during sterilization, the heat and pressure in the autoclave chamber soften the plastic and tend to warp and deform the walls of the containers.

The need to compensate for the elevated internal pressure of a plastic syringe during sterilization was recognized in U.S. Patent No. 4,718,463 which proposes to maintain a pressure in the autoclave chamber at least equal to the pressure inside the syringe.

We have surprisingly found that pre-filled plastic syringes and cartridges may be steam-sterilized by autoclaving without encountering the above-mentioned problems and without the necessity of maintaining the autoclave pressure at or above the internal pressure of the syringes and cartridges and preferably no head space in the syringes and cartridges; and providing at least 10% empty space between the plunger and the proximal end of the barrel to allow for sliding movement of the plunger toward the proximal end of the barrel in response to thermal expansion and internal vapour pressure generated during the autoclaving cycles.

Pre-filled glass syringes and cartridges having the above-described provisions relating to plastic syringes and cartridges may also be steam-sterilized using an autoclave pressure that is less than the internal pressure of the glass syringes and cartridges. However, we have found that they may also be sterilized using overpressure without the danger of plunger blow-out if the head space is minimized and sufficient plunger movement is allowed in the barrel.

It is essential however to satisfy two requirements:

(1) to maintain a head space not exceeding about 10% of the fill volume in the syringe or cartridge, and preferably no head space at all; and

(2) to provide sufficient leeway for the plunger to allow movement toward the proximal end of the barrel in response to the thermal expansion of the content in the barrel.

When these requirements are met, sterilization of pre-filled plastic syringes and cartridges by saturated steam can be accomplished under an autoclave pressure that is less than the pressure in the syringes and cartridges. In order to prevent the collapse of the steam atmosphere, the rate of cooling should be

maintained within one unit of chamber controllability, i.e., the pressure in the chamber should be one psig lower than the pressure inside the plastic syringe or the plastic cartridge. When the pre-filled syringes and cartridges are made of glass and the above-stated two requirements are met, they can be sterilized at an autoclave pressure that is less, equal to or greater than the pressure inside the glass syringes and cartridges.

The present invention therefore provides a method for terminal sterilization of a pre-filled plastic syringe containing a liquid, preferably a liquid medicament, for parenteral administration, said syringe comprising:

a syringe barrel terminating in a nozzle at its distal end, and an open or proximal end; and

a slideable plunger or piston situated in the barrel having a means to engage a plunger rod, said method comprising the steps of:

inserting the plunger into the barrel and positioning it toward the distal end thereof to leave a volume of at least about 2% empty space between the plunger and the proximal end of the barrel;

filling the syringe through its nozzle with the liquid medicament allowing for a head space not exceeding about 10% by volume and, preferably, allowing essentially no head space;

hermetically sealing the nozzle by a cap;

autoclaving the pre-filled syringe to sterilize it and its content at an autoclave pressure less than the pressure of the syringe content; and

cooling the autoclave chamber with a water cascade or nozzle spray or air draft at a rate that will not allow a sudden collapse of the steam atmosphere in the autoclave chamber.

In another embodiment the present invention provides a method for terminal sterilization of a pre-filled plastic cartridge containing a liquid, preferably a liquid medicament, for parenteral administration, said cartridge comprising:

a cartridge barrel terminating in a neck portion at its distal end adapted to receive a pierceable diaphragm, and an open or proximal end; and

a slideable plunger or piston situated in the barrel having a means to engage a plunger rod, said method comprising the steps of:

inserting the plunger into the barrel as hereinbefore described;

filling the cartridge barrel with a liquid medicament through its distal end, as hereinbefore described

hermetically sealing the distal end by a pierceable diaphragm; and

autoclaving and cooling the pre-filled cartridge as hereinbefore described.

In a further embodiment the present invention provides a method for terminal sterilization of a pre-filled glass syringe or cartridge containing a liquid, preferably a liquid medicament, for parenteral administration, wherein the autoclaving of the pre-filled syringe or cartridge to sterilize it and its content is effected at an autoclave pressure that is less than, equal to or greater than the pressure of the syringe or cartridge content, with cooling of the autoclave chamber as hereinbefore described.

According to the present invention therefore there is provided a method for terminal sterilization of a pre-filled plastic or glass syringe or cartridge containing a liquid therein, said syringe or cartridge comprising:

(a) a syringe barrel terminating in a nozzle at its distal end

or

(b) a cartridge barrel terminating in a neck portion at its distal end and adapted to receive a pierceable diaphragm;

an open or proximal end; and

a slideable plunger or piston situated in the barrel having a means to engage a plunger rod, said method comprising the steps of:

inserting the plunger into the barrel and positioning it toward the distal end thereof to leave a volume of at least about 2% empty space between the plunger and the proximal end of the barrel;

filling the syringe or barrel through its nozzle or neck portion respectively with the liquid allowing for a head space not exceeding about 10% by volume;

hermetically sealing the nozzle by a cap, or the neck

portion by a pierceable diaphragm, respectively; either

autoclaving the pre-filled plastic syringe or cartridge to sterilize it and its content at an autoclave pressure less than the pressure of the syringe or cartridge content; or

autoclaving the pre-filled glass syringe or cartridge to sterilise it and its content at an autoclave pressure less than, equal to or greater than the pressure of the syringe or cartridge content; and

cooling the autoclave chamber with a water cascade or nozzle spray or air draft at a rate that will not allow a sudden collapse of the steam atmosphere in the autoclave chamber.

Preferably the syringe or cartridge is filled with the liquid, which is preferably a liquid medicament or a contrast agent used for diagnostic examination, allowing essentially no head space, and a volume of empty space between the plunger and the proximal end of the barrel of about 5%, preferably about 10% or more. When the syringe or cartridge is plastic, the internal pressure is continuously monitored during the autoclave cycles and the pressure in the autoclave chamber is kept at least one unit of pressure controllability lower than the internal pressure of the syringe or cartridge content.

In order to maintain an autoclave pressure that is less than the internal pressure of the syringes or cartridges, the vapor pressure of the content in the syringes and cartridges at the sterilization temperature must be determined. A pressure offset is then incorporated into programmable controls having hardware and software. Such control selectively adds air during the autoclave cycle to maintain a pressure in the autoclave that is lower than the pressure of the syringe or cartridge content. For example, if a formulation generates a vapor pressure of 15.2 psig at 121.5 °C, the pressure in the autoclave chamber would be reduced to less than 15.2 psig. Examples of vapor pressure of some samples are as follows:

| Example | Sterilization Temp | Vapour Pressure, psig |
|---|---|---|
| Purified Water | 121.5 °C | 15.2 |
| Iohexol Solution 75.5% w/v | 121.5 °C | 14.7 |
| Iohexol Solution 51.77% w/v | 121.5 °C | 15.0 |

To provide the necessary control system, programmable autoclaves are commercially available (American Sterilizer Co., PA) to accomplish such controls using a temperature measuring device, such as a thermocouple, RTD or a pressure transducer, in direct contact with the content of the syringe to continuously feed data into the computer and trigger the necessary response thereto.

In the practice of the invention, when sterilizing a large number of samples in a batch-type operation, at least one temperature/pressure measuring device in direct contact with the content of one sample is necessary for monitoring the temperature and to automatically trigger a response to regulate the pressure within the autoclave. For that purpose a special syringe can be adapted which in all aspects is the same as any other syringe or cartridge, except for a built-in thermocouple, resistance temperature device (RTD) or pressure transducer connected to the hardware/software of the autoclave. Preferably, however, a statistically representative number of samples, placed at pre-determined location in the autoclave chamber, equipped with such temperature/pressure measuring device should be used.

The invention will now be described in detail with reference to the following figures, but without limitation thereto, wherein.

FIG 1. is a plan view of a hypodermic needle;

FIG. 2 is a plan view of a cartridge;

FIG. 3 is a plan view of a cap or sheath to cover the hypodermic needle shown in FIG. 1;

FIG. 4 is a plan view of a plunger or piston adapted for use in the cartridge shown in FIG. 2;

FIG 5. is a plan view of a fully assembled syringe; hypodermic needle and plunger; and

FIG. 6 is a plan view of a syringe holder having the cap, shown in FIG. 3, thereon.

Referring to the drawings, wherein like numerals are used to identify like parts, there are illustrated two embodiments of the present invention: FIG. 2 shows a cartridge and FIG. 5 shows a syringe with an attached hypodermic needle.

Shown in FIG. 2, cartridge 10 comprises: a cartridge barrel 20, formed of glass or plastic having a distal end 26 and a proximal end 40. Distal end 26 has a neck portion 28 which terminates in an opening (not shown) closed by a diaphragm cap 30 and a diaphragm 36. Diaphragm cap 30 contains an annular groove 32 to receive a snap-on hypodermic needle 60 shown in FIG. 1. Hypodermic needle 60 comprises a snap-on portion 62 which is to engage diaphragm cap 30 in a mating relationship; and a conical portion 64 which is to receive and engage proximal end 74 of cap 70. When the hypodermic needle 60 is snapped on the cartridge, the proximal end of said needle pierces the diaphragm 36 thereby providing communication between said needle and the liquid medicament 24 contained in cartridge barrel 20. The proximal end 40 of the cartridge 10 is open for receipt of a plunger or piston 50, shown in FIG. 4, which has a forward, liquid-interfacing surface 52 and a rearwardly extending threaded portion 56 for interconnection with a plunger rod (not shown) when the cartridge is readied for use.

Cartridge barrel 20 is filled with a liquid medicament 24 in such a way that: (1) a head space of no more than about 10% of the volume of the liquid is provided at the distal end 26 of the cartridge barrel 20 and; (2) at the proximal end 40 of the cartridge barrel 20 sufficient leeway is provided for the plunger to slide toward the proximal end in response to the thermal expansion of the liquid formulation contained in the

cartridge 10. Such leeway should, preferably, be about 10% or more of the volume of the liquid formulation. To insure against accidental pricking, and to protect the hypodermic needle 60 from contamination and damage, a cap or sheath 70 is provided, as shown in FIG. 3. Said cap 70 comprises a closed distal end 72 and an open proximal end 74 which is adapted to engage the conical portion 64 of hypodermic needle 60. The hypodermic needle and cap for the same may be fitted to the cartridge after the terminal sterilization process is complete.

FIG. 5 shows a syringe 10' equipped with a hypodermic needle 60' and plunger 50', and filled with a liquid medicament 24'. Syringe 10' comprises: a syringe barrel 20', formed of glass or plastic, having a distal end 26 and a proximal end 40'. Hypodermic needle 60' comprises a conical portion 64' which is to receive and engage proximal end 74' of cap 70' shown in FIG. 3. Plunger 50', having a liquid interfacing surface 52' and a rearwardly extending threaded portion 56' for interconnection with a plunger rod, is shown inserted into syringe barrel 20' at its proximal end 40'. The syringe functions analogously to the cartridge hereinbefore described.

It is important here as well as with the cartridges, that syringe barrel 20' is filled with a liquid medicament 24' in such a way that: (1) a head space of no more than about 10% is provided at the distal end 26' of the syringe barrel 20' and; (2) at the proximal end 40' of the syringe barrel 20' sufficient leeway is provided for the plunger to slide toward the proximal end in response to the thermal expansion of the liquid formulation contained in syringe 10'. Such leeway should, preferably, be about 10% or more of the volume of the liquid formulation.

The cartridge and syringe containing the liquid medicament therein, hereinbefore described, are sterilized according to the method of the present invention and are used in the conventional manner to administer their content to a patient. A convenient way to accomplish such administration is by the use of a syringe/cartridge holder, such as shown in FIG. 6. A similar holder is disclosed in U.S. Patent No. 4,585,445. The syringe/cartridge holder 80 comprises a semi-cylindrical body portion 82, a plunger rod 84, associated piston engagement means 86 and finger gripping means 88. Semi-cylindrical body portion 72 is adapted for side-loading a cartridge 10 or syringe 10' through the open side wall. The cartridge/syringe is then locked in the holder to prevent axial displacement thereof, and plunger rod 84 is engaged with plunger 56 of the cartridge (or 56' of the syringe) through piston engagement means 86. After removal of cap 70, the assembly is ready for aspirating use.

The present terminal sterilization method may be used for a variety of chemical, pharmaceutical and veterinary liquid formulations, including liquid contrast media, and is an important advance in providing pyrogen/bacteria/viral free sterile products.

While preferred embodiments of the invention have been described and illustrated in the specification and drawings, it is to be understood that such is merely illustrative of the underlying concept and features of the invention and are not to be limiting of the scope of the invention and the appended claims.

## Claims

1. A method for terminal sterilization of a pre-filled plastic or glass syringe or cartridge containing a liquid therein, said syringe or cartridge comprising:

   (a) a syringe barrel terminating in a nozzle at its distal end

   or

   (b) a cartridge barrel terminating in a neck portion at its distal end and adapted to receive a pierceable diaphragm;

   an open or proximal end; and

   a slideable plunger or piston situated in the barrel having a means to engage a plunger rod, said method comprising the steps of:

   inserting the plunger into the barrel and positioning it toward the distal end thereof to leave a volume of at least about 2% empty space between the plunger and the proximal end of the barrel;

   filling the syringe or barrel through its nozzle or neck portion respectively with the liquid allowing for a head space not exceeding about 10% by volume;

   hermetically sealing the nozzle by a cap, or the neck

   portion by a pierceable diaphragm, respectively; either

   autoclaving the pre-filled plastic syringe or cartridge to sterilize it and its content at an autoclave pressure less than the pressure of the syringe or cartridge content; or

   autoclaving the pre-filled glass syringe or cartridge to sterilise it and its content at an autoclave pressure less than, equal to or greater than the pressure of the syringe or cartridge content; and

   cooling the autoclave chamber with a water cascade or nozzle spray or air draft at a rate that will

not allow a sudden collapse of the steam atmosphere in the autoclave chamber.

2. A method as claimed in claim 1 wherein said syringe or cartridge is filled with said liquid allowing essentially no head space.

3. A method as claimed in claim 1 wherein the volume of empty space between the plunger and the proximal end of the barrel is about 5%.

4. A method as claimed in claim 1 wherein the volume of empty space between the plunger and the proximal end of the barrel is about 10%.

5. A method as claimed in any one of the preceding claims wherein said plunger is adapted to move toward the proximal end of the barrel in response to thermal expansion and internal vapor pressure of the liquid contained therein.

6. A method as claimed in any one of the preceding claims wherein said liquid is a liquid medicament.

7. A method as claimed in any one of claims 1 to 5 wherein said liquid comprises a contrast agent used for diagnostic examination.

8. A method as claimed in any one of the preceding claims wherein when the syringe or cartridge is plastic the internal pressure is continuously monitored during the autoclave cycles and the pressure in the autoclave chamber is kept at least one unit of pressure controllability lower than the internal pressure of the syringe or cartridge content.

FIG. 1

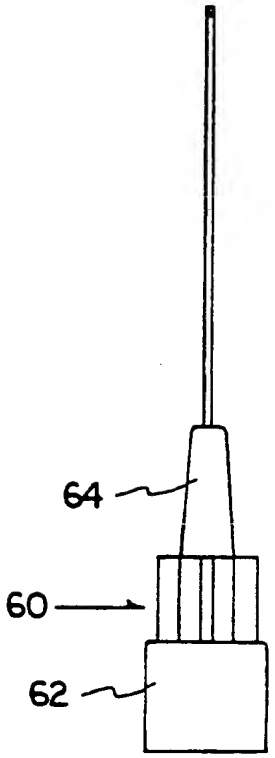



FIG. 2

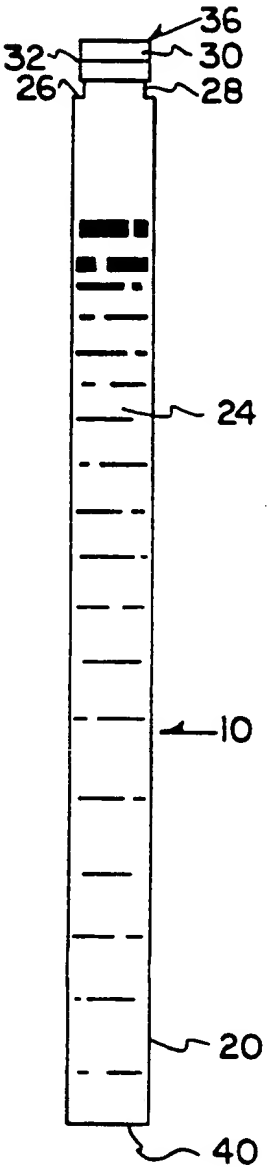



FIG. 3

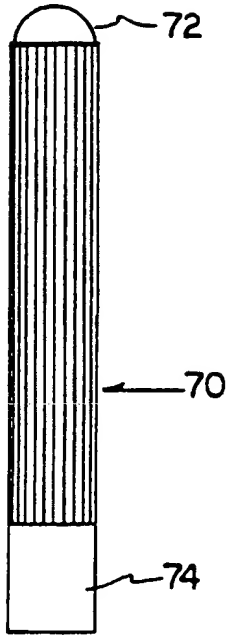



FIG. 4

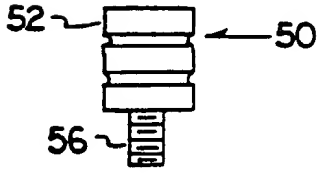


FIG. 5

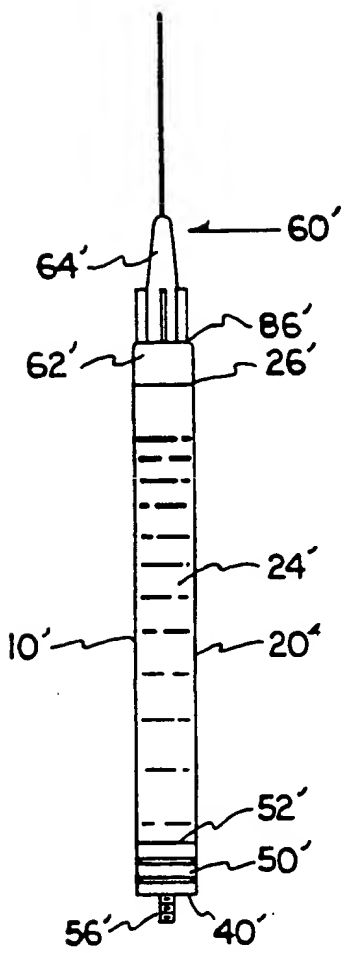
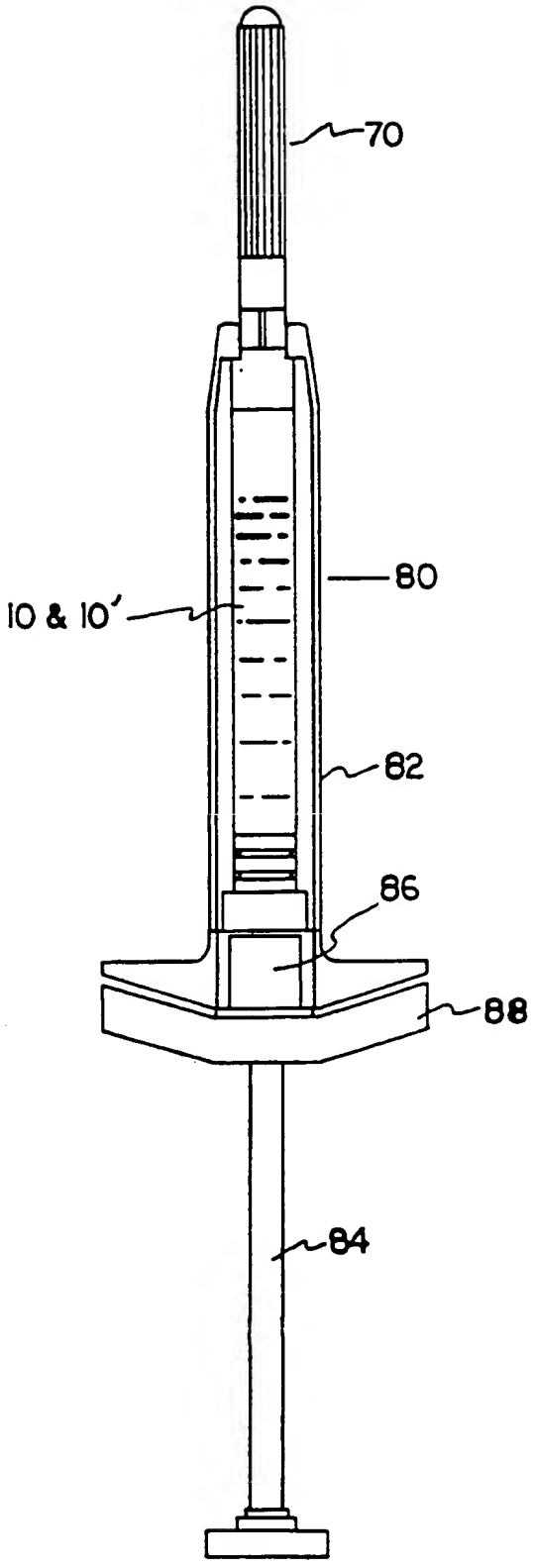


FIG.6



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# EUROPEAN SEARCH REPORT

Application Number

EP 93 20 0192

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
|---|---|---|---|
| A<br>D | EP-A-0 227 401 (MALLINCKRODT, INC)<br>* the whole document *<br>& US-A-4 718 463 | 1-8 | A61L2/06 |
| A | FR-A-2 258 866 (INSTITUT MERIEUX) | | |
| A | GB-A-2 201 392 (GREATER GLASGOW HEALTH BOARD) | | |
| A | DE-A-2 415 963 (AKTIEBOLAGET ELECTROLUX) | | |
| | | | TECHNICAL FIELDS SEARCHED (Int. Cl.5) |
| | | | A61L |

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 26 APRIL 1993 | G.COUSINS-VAN STEEN |

CATEGORY OF CITED DOCUMENTS

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